Express Mail Label No.: EV392125020US
Date of Deposit: November 30, 2004

Attorney Docket No. 22596-531

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S):	Jiang *et al.*		
SERIAL NO.:	09/975,776	EXAMINER:	Frederick F. Krass
FILING DATE:	October 10, 2001	ART UNIT:	1614
FOR:	PHARMACEUTICAL COMPOSITIONS CONTAINING β-LAPACHONE, OR DERIVATIVES OR ANALOGS THEREOF, AND METHODS OF USING SAME		

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. DASHARATHA REDDY UNDER 37 C.F.R. §1.132

I, DASHARATHA REDDY, of 11C Railroad Street, Acton, MA, declare and state that:

1. I am a co-inventor, together with Zhiwei Jiang, of the subject matter claimed in the above-referenced U.S. patent application.

2. I received my M.S. degree in Chemistry from Kakatiya University, Warangal, India in 1983 and my Ph.D. degree in Organic Chemistry from Indian Institute of Science, Bangalore, India in 1988. I worked as a post-doctoral fellow at Northwestern University, Evanston, Illinois.

3. I am presently employed by ArQule, Inc. (formerly Cyclis Pharmaceuticals, Inc.), 19 Presidential Way, Woburn, Massachusetts, the assignee of the above-referenced patent application. I have been employed by ArQule, Inc. for 3 years. Since the beginning of my career, I have developed novel compositions and methods of preparing solubilizing formulations for different anti-cancer drugs including, β-lapachone and its analogs and derivatives. I have more than 25 publications in the field of anti-cancer drug chemistry.

4. I have reviewed the Final Office Action dated August 25, 2004. I understand that

claims 1, 2, 6, 9, 11, 12, 15, 18, 19, 21, 22, 25, 28, 30-34, 36, 37, 40, 43, 45-48, 51, 54, 180, 182-186 and 204-209 have been rejected under 35 U.S.C. §103(a) as being unpatentable over WO 00/61142 to Pardee ("Pardee"), taken in view of U.S. Patent No. 4,983,586 to Bodor ("Bodor").

5. I have reviewed the present application in conjunction with the Pardee and Bodor references.

6. I make this declaration to rebut the Examiner's assertion, with which I do not agree. It is my opinion that the pending claims are not obvious in view of the combination of Pardee and Bodor. The Examiner asserts that it would have been obvious to have solubilized the anti-neoplastic/anti-tumor agents of the primary reference (β-lapachone and taxol) by complexing them with hydroxypropyl-beta-cyclodextrin of the secondary reference to improve solubility for parenteral administration. To the contrary, one of ordinary skill in the art would not be motivated to combine Pardee and Bodor nor would one of ordinary skill in the art have a reasonable expectation of success combining the teachings of Pardee and Bodor to reach the presently claimed invention. Further, the combination of Pardee and Bodor could not lead the ordinary skilled artisan to the unexpected and superior advantages (increased stability of β-lapachone) that the claimed invention provides.

7. The present invention as claimed is directed to pharmaceutical compostions, formulations and kits comprising a therapeutically effective amount of β-lapachone or analogs and derivatives thereof and the solubilizing carrier molecule beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin. There is no suggestion or motivation to combine Pardee and Bodor to reach the present invention. The Examiner asserts that the skilled artisan would combine Pardee and Bodor to reach the present invention because of the related biological activity of β-lapachone and paclitaxel disclosed in Pardee and the compounds disclosed in Bodor (anti-neoplastic/anti-tumor activity). This is incorrect. One of ordinary skill in the art would readily recognize that biological activity is not a determinate of whether a water-insoluble compound (*e.g.*, β-lapachone, paclitaxel, etc.) would complex with a

solubilizing carrier molecule (*e.g.*, beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin); but rather, would recognize that it is the chemical structure and chemical properties of the water-insoluble compound that are the key determinates to be considered in determining complexation and resulting solubilization of the water-insoluble compound in the solubilizing carrier molecule. Thus, in the instant claimed invention, it is the chemical structure and chemical properties of β-lapachone and the compatibility of those features with the beta-cyclodextrin molecule that will determine the solubility of the complex and its therapeutic utility.

8. β-lapachone (3,4-dihydro-2,2-dimethyl-2H-naphtho [1,2-b]pyran-5,6-dione) is a member of the quinone family of molecules and is derived from the napthoquinone, lapachol. Studies have indicated that several features of the β-lapachone chemical structure are critical to its water solubility; such as, β-lapachone is a molecule having an angular ring system and β-lapachone contains a ortho-quinone system at positions 5 and 6 and a ether linkage at position 2 (Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). Therefore, it is the interaction between these critical structural features of the β-lapachone molecule and the essential solubilizing features of the beta-cyclodextrin molecules that will determine the possibly solubility of the formed complex and its resulting therapeutic utility.

   Cyclodextrins are oligosaccharides containing toroidal, hydrophobic central cavity and a hydrophilic outer surface The most common cyclodextrins are α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin. The main differences between these molecules is the amount of glucopyranose units each contains and the size of the central cavity. The central cavity size is 4.7-5.3 angstroms, 6.0-6.5 angstroms and 7.5-8.3 angstroms for the cyclodextrins, respectively (U.S. Patent No. 6,407,079; Croft et al., *Tetrahedron* 39(9):1417-74, 1983; Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003).

   The central cavity of the cyclodextrin molecule is lipophilic as it is lined with skeletal carbons and ethereal oxygens of glucose residues (Fromming et al., *Cyclodextrins in Pharmacy*, Kluwer Acad. Publ., Dordrecht, 1994; Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). The polarity of the cavity is similar to that of aqueous ethanolic solution (Fromming et al., *Cyclodextrins in Pharmacy*, Kluwer

Acad. Publ., Dordrecht, 1994). This lipophilic microenvironment is accessible by suitably sized and charged molecules (Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). While prediction of compound solubilization by cyclodextrins is highly empirical, it is known that aqueous soluble drugs do not readily complex with cyclodextrins (Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). This is the result of specific thermodynamic parameters that must be met for cyclodextrin/drug complexation (Rekharsky et al., *J. Phys. Chem.* 98:4098-4103, 1994; Rekharsky et al., *J. Phys. Chem.* 98:10282-88, 1994; Rekharsky et al., *J. Am. Chem. Soc.* 117:8830-40, 1995). Specifically, it appears that main driving force for complex formation is the release of enthalpy-rich water from the cyclodextrin cavity rendering an environment suitable for hydrophobic, non-aqueous soluble drugs (Mendard et al., *Drug Dev. Ind. Pharm.* 16:91-113, 1990). However, it also appears that for drug-cyclodextrin complexation other forces; such as, van der Waals interactions, hydrogen bonding, hydrophobic interactions, release of cyclodextrin ring strain and solvent-surface tension changes other forces are important (Nishijo et al., *J. Pharm. Sci.* 80:58-62, 1990; Cramer, *Angew. Chem.* 68:115-120, 1956; Tong et al., *Pharm. Res.* 8:951-57, 1991; Jones et al., *Acta Pharm. Technol.* 30:213-23, 1984; Tabushi et al., *J. Am. Chem. Soc.* 100:916-19, 1978; Orstan et al., *Int. J. Pharm.* 80:243-51, 1993).

It is clear that the interaction between the chemical structure and properties (*e.g.*, geometry, hydrophobicity, etc.) of the water-insoluble drug (*e.g.* β-lapachone or analogs and derivatives thereof, paclitaxel, etc.) and the cyclodextrin molecule (*e.g.* beta-cyclodextrin molecules) and the compatibility of the drug to satisfy these parameters of the cyclodextrin molecule are critical to determine if the solubility of drug of interest can be enhanced by complexation with the cyclodextrin molecule.

9. I disagree with the Examiner's assertion that the skilled artisan would combine Pardee and Bodor because Bodor contemplates at least 57 anti-tumor agents which can be solubilized in hydroxypropyl-beta-cyclodextrin and β-lapachone is a water-insoluble, anti-tumor compound.

   The skilled artisan reading Bodor would recognize that none of the contemplated anti-tumor compounds disclosed therein are members of the ortho-quinone family of molecules or derived from napthoquinones. Further, while a few compounds have an

angular ring system (*i.e.*, meogarol, homoharringtonine, levonantradol, vincristine, vinblasine) and a few other compounds have an ether linkage, albeit in a sugar moiety (*i.e.*, Ara-AC, Ara-C, dihydro-5-azacytidine, tiazofurin, sangivamycin, cytosine arabinoside, 6-mercaptopurine, etoposide and teniposide), none of the contemplated anti-neoplastic compounds of Bodor have an ortho-quinone system and certainly none of the disclosed compounds comprise all the structural features essential to the water-solubility of β-lapachone (angular ring system, ortho-quinone system and a ether linkage). *See*, Appendix A.

10. As a result of the lack of structural similarity between the compounds of Pardee and the compounds of Bodor, the only suggestion or motivation to combine Pardee and Bodor is the anti-neoplastic activity of the disclosed compounds, which, as described in the prior art, is not determinative of drug/carrier complexation or solubilization potential. In fact, the prior art teaches that not all compounds with anti-neoplastic activity can be solubilized and therapeutically effective when complexed with beta-cyclodextrin molecules. For example, Pardee discloses two compounds which are water-insoluble and have anti-tumor biological activity, β-lapachone and paclitaxel, and further teaches that these two compounds are readily solubilized and therapeutically effective when complexed with lipiodol. While paclitaxel is water-insoluble and has anti-neoplastic/anti-tumor activity similar to β-lapachone, these compounds have very different chemical structures.

    Relying on the Examiner's assertion that it would be obvious to solubilize water-insoluble, anti-neoplastic/anti-tumor agents in beta-cyclodextrin molecules based on the combination of Pardee and Bodor, one would expect paclitaxel to be readily solubilized and therapeutically effective when complexed to beta-cyclodextrin molecules, similar to β-lapachone since both compounds are water-insoluble and have anti-neoplastic/anti-tumor activity, even though they have different chemical structures. This is not the case. Studies have shown that paclitaxel, a water-insoluble, anti-neoplastic/anti-tumor agent, is not solubilized and therapeutically effective in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin (Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). As only one of the two water-insoluble, anti-neoplastic/anti-tumor compounds disclosed in Pardee is solubilized and therapeutically effective in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin

disclosed by Bodor, there is no suggestion or motivation to combine Pardee and Bodor and that one of ordinary skill in the art would recognize that the combination of Pardee and Bodor would not render a reasonable expectation of success.

11. Moreover, Bodor teaches away from the present invention. Of the myriad of water-insoluble, anti-neoplastic compounds known in the art, Bodor merely contemplates approximately 57 compounds and only provides working examples for solubilizing only four (Methotexate, Chlorambucil, Lomustine and Melphalan) in hydroxypropyl-beta-cyclodextrin. *See*, Col. 76, lines 44-49; Col. 77, Table III; Col. 76, line 65 – Col. 79, line 44 including Tables V – VIII. Besides these four working examples, the remaining anti-neoplastic compounds disclosed in Bodor are purely prophetic and that, in fact, several of these contemplated anti-neoplastic compounds are not readily solubilized in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin (*i.e.*, desmethylmisonidazole, Ara-C, hydroxyurea, 5-fluorouracil, 6-mercaptopurine, 5-methylthtrahydrohomofolic acid, SR-2555, SR-2580, bactobolin, acivicin, streptozotocin). Specifically, these compounds are known in the art to be water-soluble. *See*, Appendix B.

As stated in the art, the lipophilic microenvironment of the beta-cyclodextrin molecule is accessable by suitably sized and charged molecules and that water-soluble drugs do not readily complex with cyclodextrins due to specific thermodynamic parameters that must be met for cyclodextrin/drug complexation (Rekharsky et al., *J. Phys. Chem.* 98:4098-4103, 1994; Rekharsky et al., *J. Phys. Chem.* 98:10282-88, 1994; Rekharsky et al., *J. Am. Chem. Soc.* 117:8830-40, 1995; Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). Thus, this data shows that several species of the genus of anti-neoplastic compounds disclosed in Bodor are unable to complex and enhance their solubility with beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin molecules and is evidence that the skilled artisan in view of the prior art would readily recognize the limitations of the teachings of Bodor and would restrict those teachings to only the enhanced solubility of Methotexate, Chlorambucil, Lomustine and Melphalan in hydroxypropyl-beta-cyclodextrin as described in the working examples. Thus, there is no suggestion or motivation to combine Pardee and Bodor to reach the present invention

12. I disagree with the Examiner's statement that the linear relationship observed between solubility and increase in hydroxypropyl-beta-cyclodextrin concentration is not unexpected. The complexation of β-lapachone with beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin was expected to produce a typical B-type phase solubility curve (Higuchi and Connors, *Adv. Anal. Chem. Instrum.* 4:117-212 (1965)) and not the A1-type phase solubility curve that was actually produced, which denoted the surprising linear increase in solubility. In fact, studies have shown that when β-lapachone is complexed with alpha-cyclodextrin, beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin or gamma-cyclodextrin only complexation with beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin resulted in linear increases in solubility which resulted in therapeutic effectiveness. Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003. The skilled artisan would readily recognize based on the teachings in the art that the varied relationship observed between drug solubility and increase in solubilizing carrier concentration among members of the cyclodextrin family show that the linear relationship observed between solubility and increase in beta-cyclodextrin and hydroxypropyl-beta-cyclodextrin concentration is unexpected.

13. The teachings in the art in combination with the evidence presented in the instant application show that the evidence in the specification is not applicable only to hydroxypropyl-beta-cyclodextrin but also to beta-cyclodextrin. Specifically, hydroxypropyl-beta-cyclodextrin is obtained by treating a base-solubilized solution of beta-cyclodextrin with propylene oxide thereby modifying the hydrophilic outer surface which increases aqueous solubility well in excess of 60% (w/v). Pitha et al., *Int. J. Pharm.* 29:73-82, 1986. As described in the art, it is known that the central, lipophilic cavity of the cyclodextrin molecule that is critical for the complex formation between the cyclodextrin molecule and the water-insoluble drug candidate (Fromming et al., *Cyclodextrins in Pharmacy*, Kluwer Acad. Publ., Dordrecht, 1994; Rekharsky et al., *J. Phys. Chem.* 98:4098-4103, 1994; Rekharsky et al., *J. Phys. Chem.* 98:10282-88, 1994; Rekharsky et al., *J. Am. Chem. Soc.* 117:8830-40, 1995) and recent studies have shown it is the interaction of the drug candidate and the central cavity of the cyclodextrin molecule which results in drug stability. Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003. As the structure of the inner cavity is unchanged by the treatment of beta-cyclodextrin with propylene oxide and

modification of the hydrophilic outer surface to produce hydroxypropyl-beta-cyclodextrin, one of ordinary skill in the art would readily recognize that complexation of β-lapachone in either beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin, which share identical central cavity structural parameters, surprisingly improves the stability of β-lapachone to photoreduction.

14. I disagree with the Examiner's assertion that motivation exists to engage in routine experimentation to find alternative solubilizing agents for β-lapachone despite the fact that β-lapachone had been solubilized in lipiodol in Pardee, solving a long-felt but unsolved need in the art (*i.e.*, problem of β-lapachone insolubility). Using references available on the filing date of the instant application, an innumerable amount of solubilizing agents are potentially useful for solubilizing water-insoluble, anti-neoplastic agents; including but not limited to, polyethylene glycol, cremephor EL, poly-L-gultamic acid, polyoxyethylene hardened castor oil, polysorbate 80, nicotinamide, polyoxyethylenesorbitan monolaurate, Macrogol and castor oil fatty acid ethyl ester (Badary, et al. *Anticancer Drugs*. 9(9):809-15, 1998; Das et al. *J. Biomed. Mater Res.* 55(1):96-103, 2001; Zou et al. *Int J Oncol.* 18(2):331-6, 2001 and U.S. Patent No. 5,846,969.

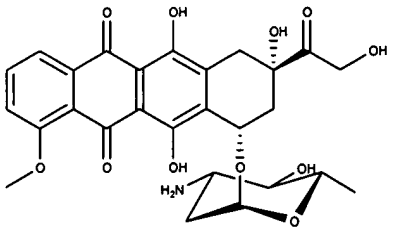
Based on the teachings in the art, the skilled artisan would recognize that the experimentation necessary to find and use the cyclodextrins of the Bodor reference with the β-lapachone compounds of the Pardee reference would have not been routine. In fact, to use the simple tests of Bodor referred to by the Examiner, without the teachings of the instant application, one of ordinary skill in the art would have to try most or all of the available agents recognized for solubilizing neoplastic agents and try each of numerous possible choices until one possibly arrived at a successful result. Reaching the claimed invention without the teachings of the instant application would involve more than routine experimentation, and for each agent tested, would not have a reasonable expectation of success. Moreover, there is no specific suggestion or motivation within Pardee and Bodor or within the nature of the problem to be solved (Pardee solved the long standing problem in the art) to solubilize β-lapachone with beta-cyclodextrin. One of ordinary skill in the art would have no reasonable expectation of success combining the teachings of Pardee and Bodor to reach the presently claimed invention.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

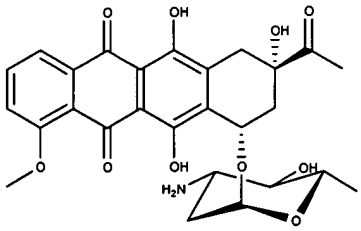
Dasharatha Reddy, Ph.D.

Signed this day 30 of November, 2004

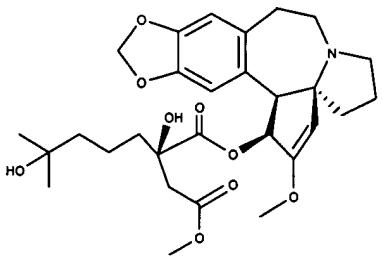
APPENDIX A



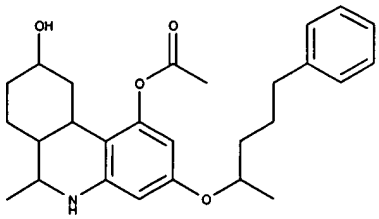
Adriamycin (doxorubicin)



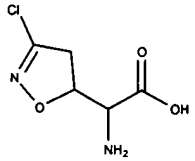
Daunomycin (daunorubicin)



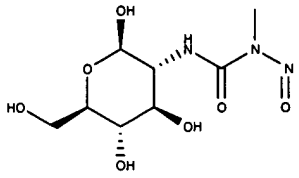
Homoharringtonine



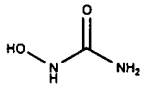
Levonantradol



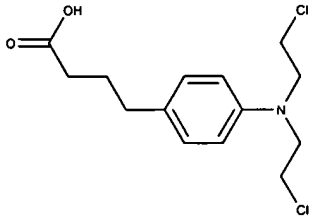
Acivicin



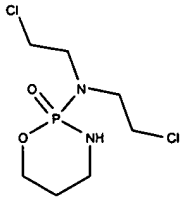
Streptozotocin



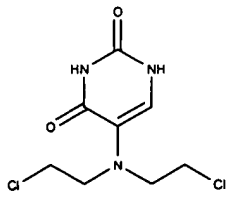
Hydroxyurea



Chloroambucil

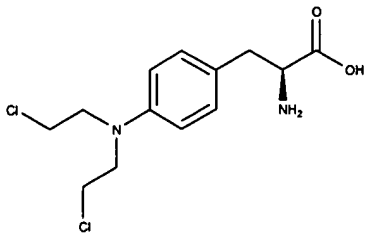


Cyclophosphamide

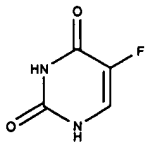


Uracil mustard

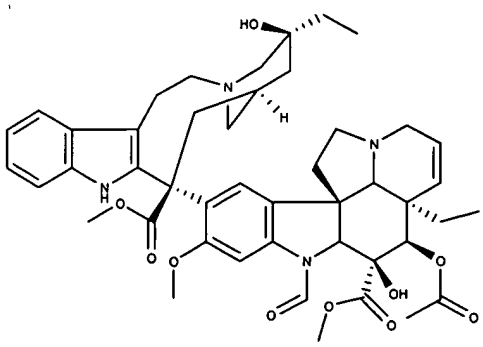
APPENDIX A



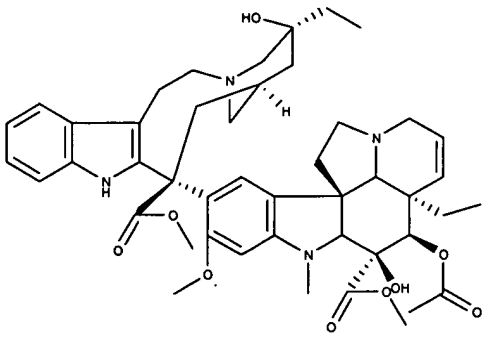
Melphalan



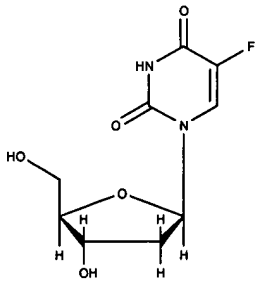
5-Fluorouracil (5-FU)



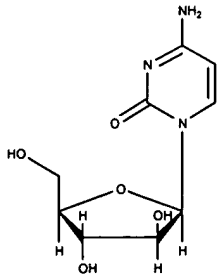
Vincristine



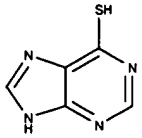
Vinblastine



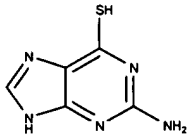
Floxuridine (5-FUDR)



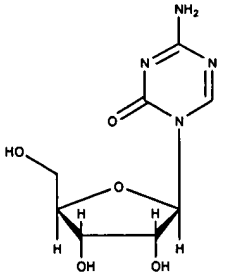
Cytosine Arabinoside



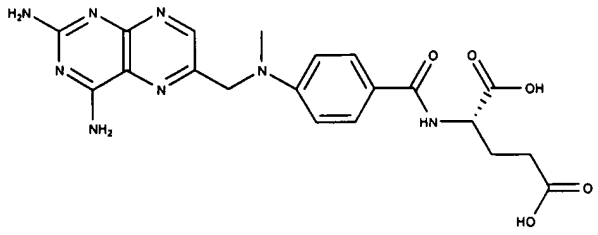
6-Mercaptopurine



Thioguanine

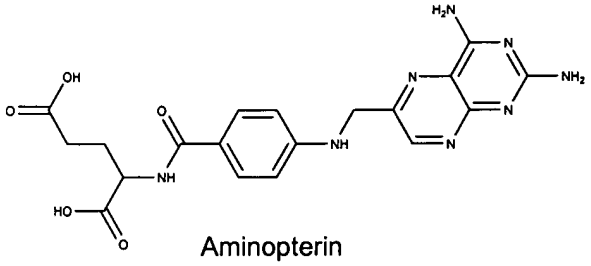


5-Azacytidine

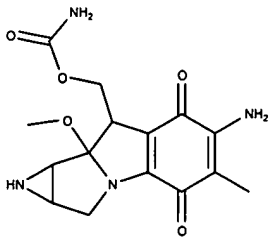


Methotrexate

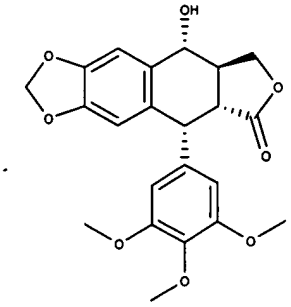
APPENDIX A



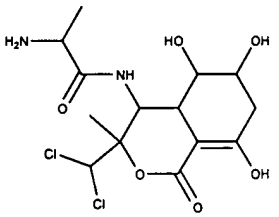
Aminopterin



Mitomycin C



Podophyllotoxin



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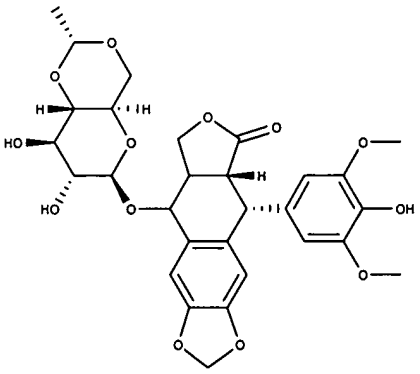
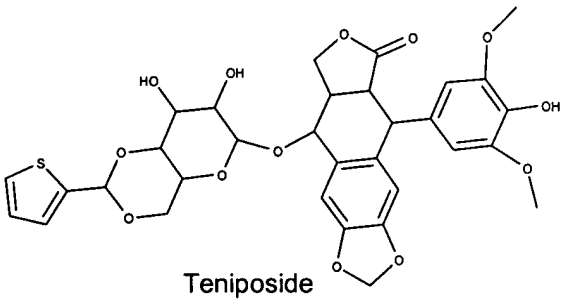
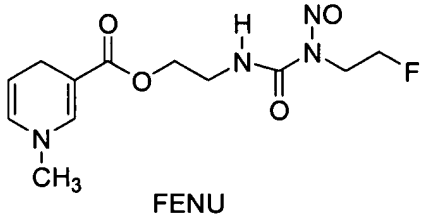


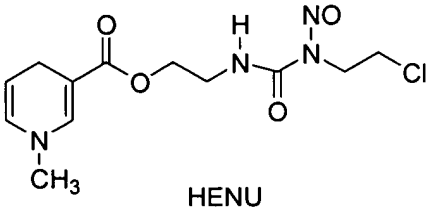
Etoposide



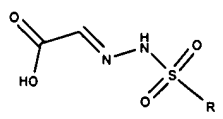
Teniposide



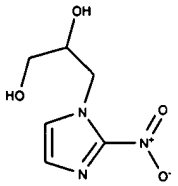
FENU



HENU

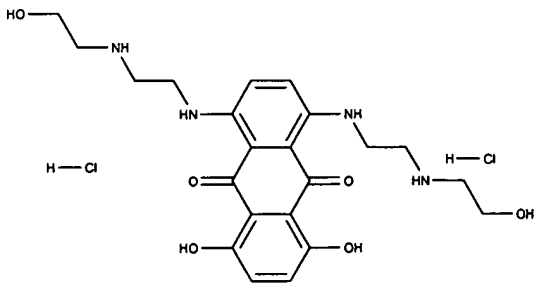


Glycoxylic acid sulfonylhydrazone

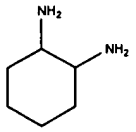


Desmethylmisonidazole

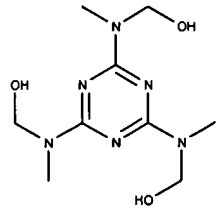
APPENDIX A



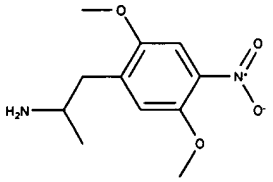
Mitoxantrone



DACH



Trimethyl TMM



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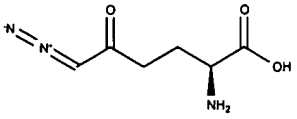
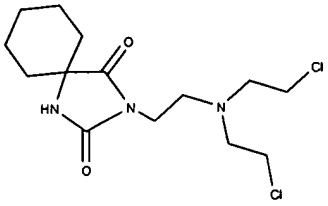
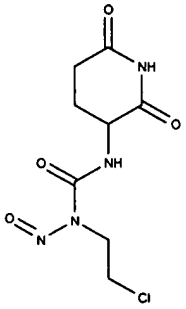


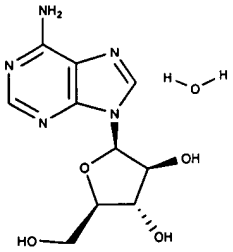
L-alanosine



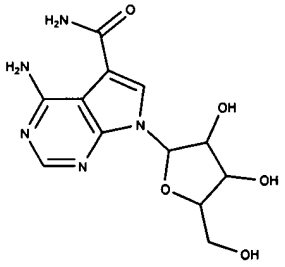
Spiromustine



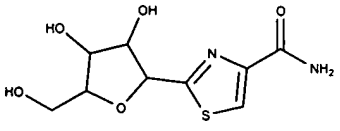
PCNU



Ara-A

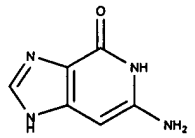


Sangivamycin

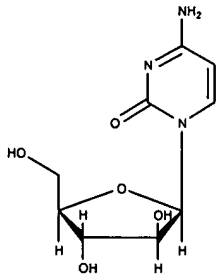


Tiazofurin

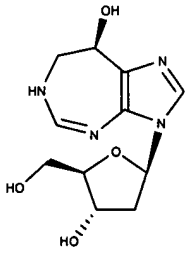
APPENDIX A



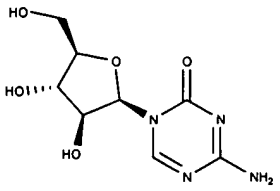
3-Deazaguanine



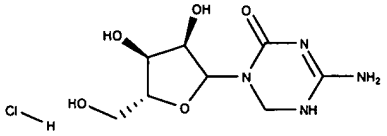
Ara-C



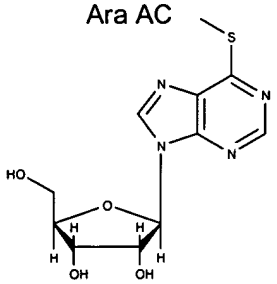
Pentostatin



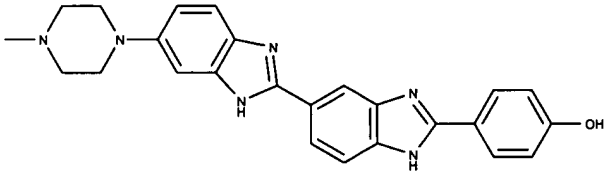
Ara AC



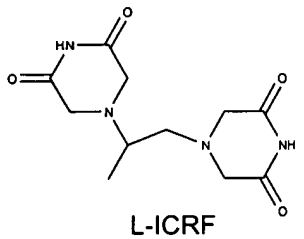
Dihydro-5-azacytidine



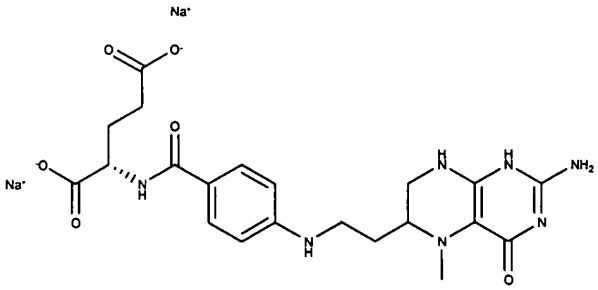
6-methylmercaptopurine ribonucleoside (6-MMPR)



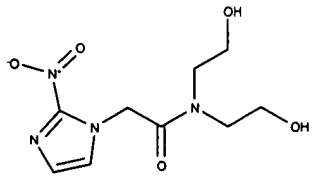
Bisbenzimidazole



L-ICRF

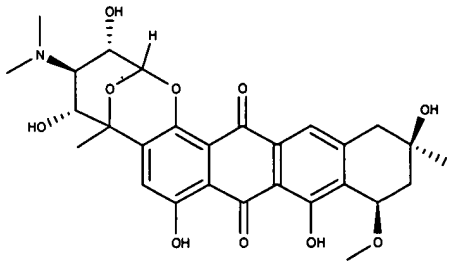


5-Methyl-tetrahydrohomofolic acid

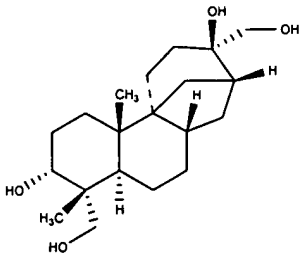


SR2555

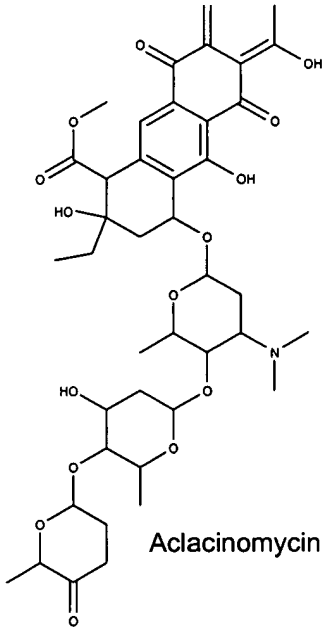
APPENDIX A



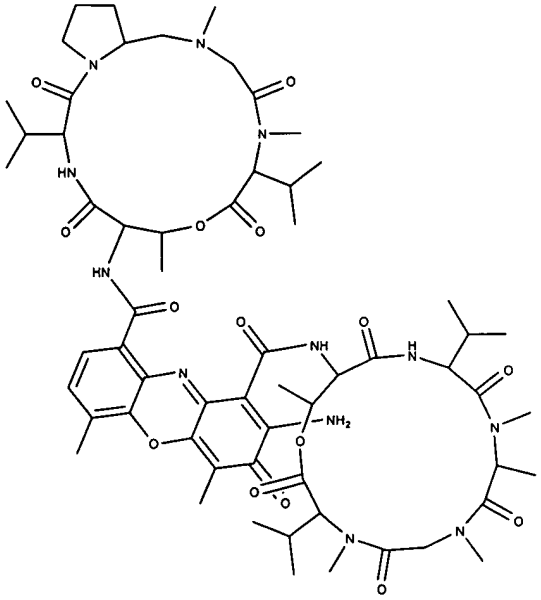
Menogarol



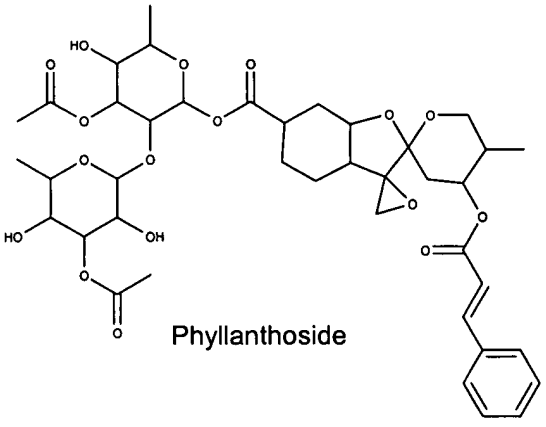
Aphidocolin



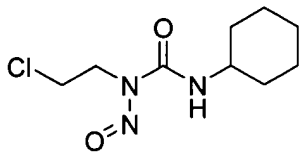
Aclacinomycin A



Dactinomycin (Actinomycin D)



Phyllanthoside



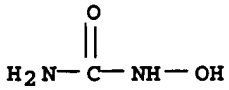
Lomustine

TRA 1977508v1

APPENDIX B

Compound: **Hydroxyurea**

Registry Number: 127-07-1



Formula: C H4 N2 O2

CA Index Name: Urea, hydroxy- (6CI,8CI,9CI)

Other Names: Biosupressin; Carbamohydroxamic acid; Carbamohydroximic acid; Carbamoyl oxime; HU; Hidrix; Hydrea; Hydreia; Hydroxycarbamide; Hydroxycarbamine; Hydroxylamine, N-(aminocarbonyl)-; Hydroxylurea; Hydroxyurea; Hydura; Hydurea; Litaler; Litalir; N-Carbamoylhydroxylamine; NCI C04831; NSC 32065; Onco-Carbide; Oxyurea; SK 22591; SQ 1089

-- Properties --

Property	Calculated Value	Condition	Note
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	1	pH 7	(1) ACD
Bioconc. Factor	1	pH 8	(1) ACD
Bioconc. Factor	1	pH 10	(1) ACD
H acceptors	4		(1) ACD
H donors	4		(1) ACD
Koc	2.42	pH 1	(1) ACD
Koc	2.50	pH 4	(1) ACD
Koc	2.50	pH 7	(1) ACD
Koc	2.49	pH 8	(1) ACD
Koc	1.96	pH 10	(1) ACD
logD	-1.81	pH 1	(1) ACD
logD	-1.80	pH 4	(1) ACD
logD	-1.80	pH 7	(1) ACD
logD	-1.80	pH 8	(1) ACD
logD	-1.91	pH 10	(1) ACD
logP	-1.800±0.187		(1) ACD
Molar Solubility	Very Soluble	pH 1	(1) ACD
Molar Solubility	Very Soluble	pH 4	(1) ACD
Molar Solubility	Very Soluble	pH 7	(1) ACD
Molar Solubility	Very Soluble	pH 8	(1) ACD
Molar Solubility	Very Soluble	pH 10	(1) ACD
Molecular Weight	76.05		(1) ACD
pKa	10.56±0.23	Most Acidic	(1) ACD

Property	Experimental Value	Condition	Note
Melting Point	141-142 °C		(2) IC

Notes:

APPENDIX B

(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)
(2) Kozyukov, V. P.; Zhurnal Obshchei Khimii 1985, V55(5), P1063-70

-- Resources --

References: ~3387

STN Files: CAPLUS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM, DIOGENES, DRUGU, EMBASE, GMELIN, HODOC, HSDB, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK, MSDS-OHS, NIOSHTIC, PHAR, PROMT, RTECS, SPECINFO, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU

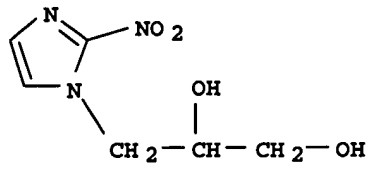
(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

Database: REGISTRY

APPENDIX B

Compound: Desmethylmisonidazole

Registry Number: 13551-92-3



Formula: C6 H9 N3 O4

CA Index Name: 1,2-Propanediol, 3-(2-nitro-1H-imidazol-1-yl)- (9CI)

Other Names: 1,2-Propanediol, 3-(2-nitroimidazol-1-yl)- (8CI); 3-(2-Nitroimidazol-1-yl)-1,2-propanediol; Demethylmisonidazole; Desmethylmisonidazole; NSC 261036; Ro 5-9963; SR 1530

-- Properties --

Property	Calculated Value	Condition	Note
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	1	pH 7	(1) ACD
Bioconc. Factor	1	pH 8	(1) ACD
Bioconc. Factor	1	pH 10	(1) ACD
Boiling Point	521.5±60.0 °C	Press: 760.0 Torr	(1) ACD
Enthalpy of Vap.	83.67±3.0 kJ/mol		(1) ACD
Flash Point	269.2±59.2 °C		(1) ACD
H acceptors	7		(1) ACD
H donors	2		(1) ACD
Koc	2.81	pH 1	(1) ACD
Koc	6.04	pH 4	(1) ACD
Koc	6.05	pH 7	(1) ACD
Koc	6.05	pH 8	(1) ACD
Koc	6.05	pH 10	(1) ACD
logD	-1.43	pH 1	(1) ACD
logD	-1.09	pH 4	(1) ACD
logD	-1.09	pH 7	(1) ACD
logD	-1.09	pH 8	(1) ACD
logD	-1.09	pH 10	(1) ACD
logP	-1.094±0.443		(1) ACD
Molar Solubility	Very Soluble	pH 1	(1) ACD
Molar Solubility	Very Soluble	pH 4	(1) ACD
Molar Solubility	Very Soluble	pH 7	(1) ACD
Molar Solubility	Very Soluble	pH 8	(1) ACD
Molar Solubility	Very Soluble	pH 10	(1) ACD
Molecular Weight	187.15		(1) ACD
pKa	13.49±0.20	Most Acidic	(1) ACD
pKa	1.06±0.33	Most Basic	(1) ACD
Vapor Pressure	1.05E-11 Torr	Temp: 25.0 °C	(1) ACD

APPENDIX B

Notes:
(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)

-- Resources --

References: ~148

STN Files: CAPLUS, BEILSTEIN, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CASREACT, CHEMCATS, CHEMLIST, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, NIOSHTIC, PHAR, PROMT, RTECS, TOXCENTER, USPATFULL

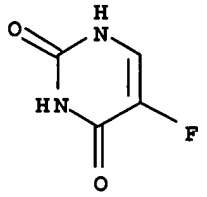
(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

Database: REGISTRY

APPENDIX B

Compound: 5-Flurouracil (5-FU)

Registry Number: 51-21-8



Formula: C4 H3 F N2 O2

CA Index Name: 2,4(1H,3H)-Pyrimidinedione, 5-fluoro- (9CI)

Other Names: Uracil, 5-fluoro- (8CI); 2,4-Dioxo-5-fluoropyrimidine; 5-FU; 5-Fluoracyl; 5-Fluoro-2,4(1H,3H)-pyrimidinedione; 5-Fluoro-2,4-pyrimidinedione; 5-Fluorouracil; Adrucil; Arumel; Carac; Carzonal; Efudex; Efudix; Efurix; FU; Fluoroblastin; Fluoroplex; Fluorouracil; Fluracil; Fluracilum; Fluri; Fluril; Ftoruracil; Kecimeton; NSC 19893; Phthoruracil; Phtoruracil; Queroplex; Ro 2-9757; Timazin; U 8953; Ulup

-- Properties --

	Calculated		
Property	**Value**	**Condition**	**Note**
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	1	pH 7	(1) ACD
Bioconc. Factor	1	pH 8	(1) ACD
Bioconc. Factor	1	pH 10	(1) ACD
H acceptors	4		(1) ACD
H donors	2		(1) ACD
Koc	8.98	pH 1	(1) ACD
Koc	8.70	pH 4	(1) ACD
Koc	1	pH 7	(1) ACD
Koc	1	pH 8	(1) ACD
Koc	1	pH 10	(1) ACD
logD	-0.78	pH 1	(1) ACD
logD	-0.79	pH 4	(1) ACD
logD	-2.29	pH 7	(1) ACD
logD	-3.27	pH 8	(1) ACD
logD	-4.73	pH 10	(1) ACD
logP	-0.779±0.311		(1) ACD
Molar Solubility	Very Soluble	pH 1	(1) ACD
Molar Solubility	Very Soluble	pH 4	(1) ACD
Molar Solubility	Very Soluble	pH 7	(1) ACD
Molar Solubility	Very Soluble	pH 8	(1) ACD
Molar Solubility	Very Soluble	pH 10	(1) ACD
Molecular Weight	130.08		(1) ACD
pKa	7.88±0.40	Most Acidic	(1) ACD

	Experimental		
Property	**Value**	**Condition**	**Note**
Melting Point	282-284 °C	Solv: methanol	(2) IC

APPENDIX B

		(67-56-1) ethyl ether (60-29-7)	
Melting Point	282-283 °C		(3) IC
Melting Point	280-282 °C (decomp)		(4) IC

Notes:
(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)
(2) Chung, Won Keun; Journal of Heterocyclic Chemistry 1983, V20(2), P457
(3) Miyashita, Osamu; Chemical & Pharmaceutical Bulletin 1981, V29(11), P3181-90
(4) Baasner, B.; Journal of Fluorine Chemistry 1989, V45(3), P417-30

-- Resources --

References: ~13718

STN Files: CAPLUS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM, DIOGENES, DRUGU, EMBASE, GMELIN, HODOC, HSDB, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK, MSDS-OHS, NIOSHTIC, PHAR, PROMT, RTECS, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU

(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

Deleted Registry Number(s): 1004-03-1, 4921-97-5, 79108-01-3

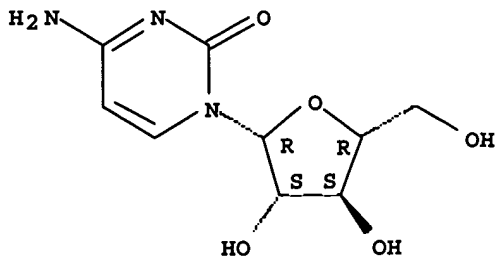
Database: REGISTRY

APPENDIX B

Compound: ARA-C

Registry Number: 147-94-4

Absolute stereochemistry.



Formula: C9 H13 N3 O5

CA Index Name: 2(1H)-Pyrimidinone, 4-amino-1-β-D-arabinofuranosyl- (9CI)

Other Names: Cytosine, 1-β-D-arabinofuranosyl- (6CI,8CI); (Arabinofuranosyl)cytosine; 1-(β-D-Arabinofuranosyl)cytosine; 1-(Arabinofuranosyl)cytosine; 1-β-Arabinofuranosylcytosine; 1-β-D-Arabinosylcytosine; 4-Amino-1-arabinofuranosyl-2-oxo-1,2-dihydropyrimidine; Ac 1075; Alexan; Ara-C; Arabinocytosine; Arabinoside C; Arabitin; Aracytidine; Aracytin; Aracytine; Arafcyt; CHX 3311; Citozar; Cyclocide; Cytarabin; Cytarabine; Cytarabinoside; Cytosar; Cytosar U; Cytosine β-D-arabinofuranoside; Cytosine β-D-arabinoside; Cytosine arabinoside; Cytosine-1-β-D-arabinofuranoside; Cytosine-1-β-arabinofuranoside; DepoCyte; Erpalfa; Iretin; NSC 287459; NSC 63878; Spongocytidine; Tarabine PFS; U 19920; U 19920A; Udicil; ara-Cytosine

-- Properties --

Property	Calculated Value	Condition	Note
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	1	pH 7	(1) ACD
Bioconc. Factor	1	pH 8	(1) ACD
Bioconc. Factor	1	pH 10	(1) ACD
Boiling Point	545.7±60.0 °C	Press: 760.0 Torr	(1) ACD
Enthalpy of Vap.	94.80±6.0 kJ/mol		(1) ACD
Flash Point	283.8±59.2 °C		(1) ACD
H acceptors	8		(1) ACD
H donors	5		(1) ACD
Koc	1	pH 1	(1) ACD
Koc	1	pH 4	(1) ACD
Koc	1.33	pH 7	(1) ACD
Koc	1.33	pH 8	(1) ACD
Koc	1.33	pH 10	(1) ACD
logD	-5.25	pH 1	(1) ACD
logD	-2.90	pH 4	(1) ACD
logD	-2.30	pH 7	(1) ACD
logD	-2.30	pH 8	(1) ACD

APPENDIX B

logD	-2.30	pH 10	(1) ACD
logP	-2.304±0.401		(1) ACD
Molar Solubility	Very Soluble	pH 1	(1) ACD
Molar Solubility	Very Soluble	pH 4	(1) ACD
Molar Solubility	Very Soluble	pH 7	(1) ACD
Molar Solubility	Very Soluble	pH 8	(1) ACD
Molar Solubility	Very Soluble	pH 10	(1) ACD
Molecular Weight	243.22		(1) ACD
pKa	13.48±0.70	Most Acidic	(1) ACD
pKa	4.47±0.45	Most Basic	(1) ACD
Vapor Pressure	3.50E-14 Torr	Temp: 25.0 °C	(1) ACD

Notes:
(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)

-- Resources --

References: ~6078

STN Files: CAPLUS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, GMELIN, HSDB, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PROMT, RTECS, TOXCENTER, USAN, USPAT2, USPATFULL, VETU

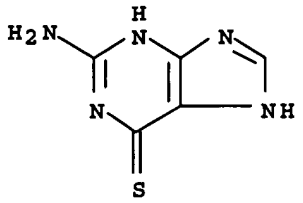
(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

Database: REGISTRY

APPENDIX B

Compound: 6-Mercaptopurine

Registry Number: 154-42-7



Formula: C5 H5 N5 S

CA Index Name: 6H-Purine-6-thione, 2-amino-1,7-dihydro- (9CI)

Other Names: Purine-6(1H)-thione, 2,3-dihydro-2-imino- (6CI); Purine-6(1H)-thione, 2-amino- (7CI,8CI); Purine-6-thiol, 2-amino- (8CI); 2-Amino-6-mercaptopurine; 2-Amino-9H-purine-6(1H)-thione; 2-Aminopurine-6-thiol; 6-Mercaptoguanine; 6-TG; 6-Thioguanine; Guanine, thio-; Lanvis; NSC 752; NSC 76504; Tabloid; Thioguanine; Tioguanin; Tioguanine

-- Properties --

Property	Calculated Value	Condition	Note
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	1	pH 7	(1) ACD
Bioconc. Factor	1	pH 8	(1) ACD
Bioconc. Factor	1	pH 10	(1) ACD
Boiling Point	555.4±42.0 °C	Press: 760.0 Torr	(1) ACD
Enthalpy of Vap.	83.67±3.0 kJ/mol		(1) ACD
Flash Point	289.7±50.2 °C		(1) ACD
H acceptors	5		(1) ACD
H donors	4		(1) ACD
Koc	1	pH 1	(1) ACD
Koc	12.1	pH 4	(1) ACD
Koc	12.5	pH 7	(1) ACD
Koc	3.58	pH 8	(1) ACD
Koc	1	pH 10	(1) ACD
logD	-2.87	pH 1	(1) ACD
logD	-0.41	pH 4	(1) ACD
logD	-0.40	pH 7	(1) ACD
logD	-0.94	pH 8	(1) ACD
logD	-2.82	pH 10	(1) ACD
logP	-0.256±0.411		(1) ACD
Molar Solubility	Very Soluble	pH 1	(1) ACD
Molar Solubility	Soluble	pH 4	(1) ACD
Molar Solubility	Soluble	pH 7	(1) ACD
Molar Solubility	Very Soluble	pH 8	(1) ACD
Molar Solubility	Very Soluble	pH 10	(1) ACD
Molecular Weight	167.19		(1) ACD

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pKa	7.44±0.40	Most Acidic	(1) ACD
pKa	3.09±0.40	Most Basic	(1) ACD
Vapor Pressure	2.25E-12 Torr	Temp: 25.0 °C	(1) ACD

Notes:
(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)

-- Resources --

References: ~1740

STN Files: CAPLUS, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, GMELIN, HODOC, HSDB, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL

(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

Deleted Registry Number(s): 611-67-6, 1125-65-1, 1832-72-0, 5632-51-9

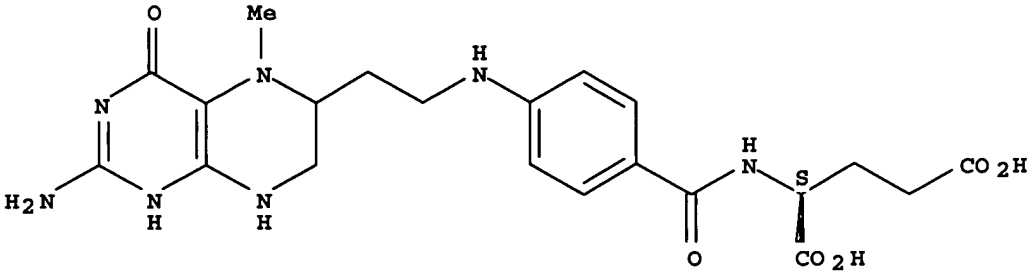
Database: REGISTRY

APPENDIX B

Compound: **5-Methyltetrahydrohomofolic acid**

Registry Number: 52196-22-2

Absolute stereochemistry.



Formula: C21 H27 N7 O6

CA Index Name: L-Glutamic acid, N-[4-[[2-(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-6-pteridinyl)ethyl]amino]benzoyl]- (9CI)

Other Names: 5-Methyltetrahydrohomofolic acid; Ketotrexate; Tetrahydro-5-methylhomofolic acid

-- Properties --

Property	Calculated Value	Condition	Note
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	1	pH 7	(1) ACD
Bioconc. Factor	1	pH 8	(1) ACD
Bioconc. Factor	1	pH 10	(1) ACD
H acceptors	13		(1) ACD
H donors	8		(1) ACD
Koc	1	pH 1	(1) ACD
Koc	1	pH 4	(1) ACD
Koc	1	pH 7	(1) ACD
Koc	1	pH 8	(1) ACD
Koc	1	pH 10	(1) ACD
logD	-6.18	pH 1	(1) ACD
logD	-4.37	pH 4	(1) ACD
logD	-5.96	pH 7	(1) ACD
logD	-6.61	pH 8	(1) ACD
logD	-6.86	pH 10	(1) ACD
logP	-1.861±1.000		(1) ACD
Molar Solubility	Very Soluble	pH 1	(1) ACD
Molar Solubility	Very Soluble	pH 4	(1) ACD
Molar Solubility	Very Soluble	pH 7	(1) ACD
Molar Solubility	Very Soluble	pH 8	(1) ACD
Molar Solubility	Very Soluble	pH 10	(1) ACD
Molecular Weight	473.48		(1) ACD
pKa	3.56±0.10	Most Acidic	(1) ACD
pKa	6.13±0.70	Most Basic	(1) ACD

APPENDIX B

Notes:
(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)

-- Resources --

References: ~21

STN Files: CAPLUS, BEILSTEIN, BIOTECHNO, CA, CANCERLIT, CHEMCATS, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PHAR, TOXCENTER, USAN, USPATFULL

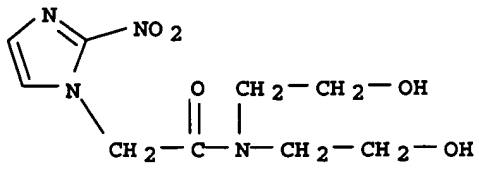
(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

Database: REGISTRY

APPENDIX B

Compound: SR 2555

Registry Number: 74141-74-5



Formula: C9 H14 N4 O5

CA Index Name: 1H-Imidazole-1-acetamide, N,N-bis(2-hydroxyethyl)-2-nitro- (9CI)

Other Names: NSC 314-055; SR 2555; TX 1892

-- Properties --

Property	Calculated Value	Condition	Note
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	1	pH 7	(1) ACD
Bioconc. Factor	1	pH 8	(1) ACD
Bioconc. Factor	1	pH 10	(1) ACD
Boiling Point	577.8±60.0 °C	Press: 760.0 Torr	(1) ACD
Enthalpy of Vap.	90.98±3.0 kJ/mol		(1) ACD
Flash Point	303.3±59.2 °C		(1) ACD
H acceptors	9		(1) ACD
H donors	2		(1) ACD
Koc	1.29	pH 1	(1) ACD
Koc	1.86	pH 4	(1) ACD
Koc	1.86	pH 7	(1) ACD
Koc	1.86	pH 8	(1) ACD
Koc	1.86	pH 10	(1) ACD
logD	-2.19	pH 1	(1) ACD
logD	-2.04	pH 4	(1) ACD
logD	-2.04	pH 7	(1) ACD
logD	-2.04	pH 8	(1) ACD
logD	-2.04	pH 10	(1) ACD
logP	-2.037±0.460		(1) ACD
Molar Solubility	Very Soluble	pH 1	(1) ACD
Molar Solubility	Very Soluble	pH 4	(1) ACD
Molar Solubility	Very Soluble	pH 7	(1) ACD
Molar Solubility	Very Soluble	pH 8	(1) ACD
Molar Solubility	Very Soluble	pH 10	(1) ACD
Molecular Weight	258.23		(1) ACD
pKa	0.63±0.31	Most Basic	(1) ACD
Vapor Pressure	3.42E-14 Torr	Temp: 25.0 °C	(1) ACD

Notes:
(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)

APPENDIX B

-- Resources --

References: ~34

STN Files: CAPLUS, BIOSIS, BIOTECHNO, CA, CANCERLIT, DDFU, DRUGU, EMBASE, MEDLINE, NIOSHTIC, PHAR, RTECS, TOXCENTER, USPATFULL

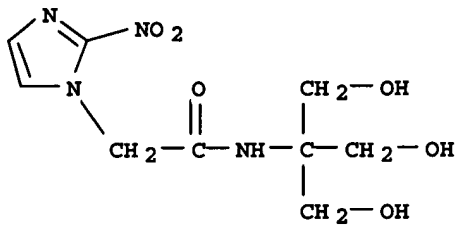
(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

Database: REGISTRY

APPENDIX B

Compound: SR 2580

Registry Number: 81892-69-5



Formula: C9 H14 N4 O6

CA Index Name: 1H-Imidazole-1-acetamide, N-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]-2-nitro- (9CI)

Other Names: NSC 328805; SR 2580; TX 1904

-- Properties --

Property	Calculated Value	Condition	Note
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	1	pH 7	(1) ACD
Bioconc. Factor	1	pH 8	(1) ACD
Bioconc. Factor	1	pH 10	(1) ACD
H acceptors	10		(1) ACD
H donors	4		(1) ACD
Koc	2.16	pH 1	(1) ACD
Koc	2.67	pH 4	(1) ACD
Koc	2.67	pH 7	(1) ACD
Koc	2.67	pH 8	(1) ACD
Koc	2.66	pH 10	(1) ACD
logD	-1.84	pH 1	(1) ACD
logD	-1.75	pH 4	(1) ACD
logD	-1.75	pH 7	(1) ACD
logD	-1.75	pH 8	(1) ACD
logD	-1.75	pH 10	(1) ACD
logP	-1.747±0.791		(1) ACD
Molar Solubility	Very Soluble	pH 1	(1) ACD
Molar Solubility	Very Soluble	pH 4	(1) ACD
Molar Solubility	Very Soluble	pH 7	(1) ACD
Molar Solubility	Very Soluble	pH 8	(1) ACD
Molar Solubility	Very Soluble	pH 10	(1) ACD
Molecular Weight	274.23		(1) ACD
pKa	12.39±0.46	Most Acidic	(1) ACD
pKa	0.37±0.31	Most Basic	(1) ACD

Notes:
(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)

APPENDIX B

-- Resources --

References: ~3

STN Files: CAPLUS, CA, TOXCENTER

(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

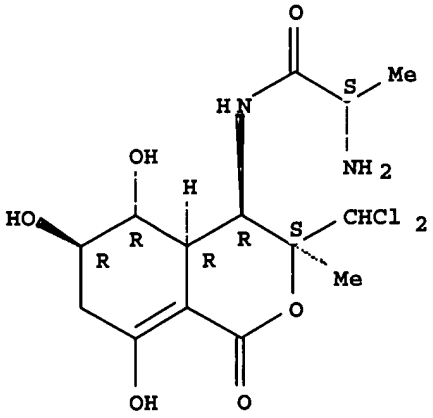
Database: REGISTRY

APPENDIX B

Compound: **Bactobolin**

Registry Number: 72615-20-4

Absolute stereochemistry.



Formula: C14 H20 Cl2 N2 O6

CA Index Name: Propanamide, 2-amino-N-[(3S,4R,4aR,5R,6R)-3-(dichloromethyl)-3,4,4a,5,6,7-hexahydro-5,6,8-trihydroxy-3-methyl-1-oxo-1H-2-benzopyran-4-yl]-, (2S)- (9CI)

Other Names: Propanamide, 2-amino-N-[3-(dichloromethyl)-3,4,4a,5,6,7-hexahydro-5,6,8-trihydroxy-3-methyl-1-oxo-1H-2-benzopyran-4-yl]-, [3S-[3α,4α(R*),4aβ,5β,6α]]-; (-)-Bactobolin; Antibiotic BN 183B; Bactobolin; NSC 325014; Y 12278

-- Properties --

Property	Calculated Value	Condition	Note
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	1	pH 7	(1) ACD
Bioconc. Factor	1	pH 8	(1) ACD
Bioconc. Factor	1	pH 10	(1) ACD
Boiling Point	683.0±55.0 °C	Press: 760.0 Torr	(1) ACD
Enthalpy of Vap.	114.59±6.0 kJ/mol		(1) ACD
Flash Point	366.8±56.7 °C		(1) ACD
H acceptors	8		(1) ACD
H donors	6		(1) ACD
Koc	1	pH 1	(1) ACD
Koc	1	pH 4	(1) ACD
Koc	1	pH 7	(1) ACD
Koc	1	pH 8	(1) ACD
Koc	1	pH 10	(1) ACD
logD	-3.62	pH 1	(1) ACD
logD	-3.36	pH 4	(1) ACD
logD	-3.02	pH 7	(1) ACD
logD	-3.24	pH 8	(1) ACD
logD	-4.45	pH 10	(1) ACD

APPENDIX B

logP	-0.518±0.652		(1) ACD
Molar Solubility	Very Soluble	pH 1	(1) ACD
Molar Solubility	Very Soluble	pH 4	(1) ACD
Molar Solubility	Very Soluble	pH 7	(1) ACD
Molar Solubility	Very Soluble	pH 8	(1) ACD
Molar Solubility	Very Soluble	pH 10	(1) ACD
Molecular Weight	383.22		(1) ACD
pKa	4.50±1.00	Most Acidic	(1),(2) ACD
pKa	8.06±0.29	Most Basic	(1),(2) ACD
Vapor Pressure	1.34E-21 Torr	Temp: 25.0 °C	(1) ACD

Notes:
(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)
(2) A significant difference may occur between experimental and calculated values.

-- Resources --

References: ~42

STN Files: CAPLUS, BEILSTEIN, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CASREACT, DDFU, DRUGU, EMBASE, IPA, MEDLINE, NAPRALERT, PHAR, RTECS, TOXCENTER, USPATFULL

(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

Deleted Registry Number(s): 77029-53-9

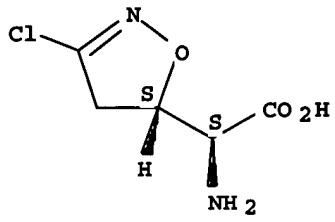
Database: REGISTRY

APPENDIX B

Compound: **Acivicin**

Registry Number: 42228-92-2

Absolute stereochemistry.



Formula: C5 H7 Cl N2 O3

CA Index Name: 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (αS,5S)- (9CI)

Other Names: 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, [S-(R*,R*)]-; (α-S, 5S)-α-Amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid; AT 125; Acivicin; Antibiotic AT 125; NSC 163501; U 42126

-- Properties --

Property	Calculated Value	Condition	Note
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	1	pH 7	(1) ACD
Bioconc. Factor	1	pH 8	(1) ACD
Bioconc. Factor	1	pH 10	(1) ACD
Boiling Point	341.6±47.0 °C	Press: 760 Torr	(1) ACD
Enthalpy of Vap.	64.32±6.0 kJ/mol		(1) ACD
Flash Point	160.4±52.7 °C		(1) ACD
H acceptors	5		(1) ACD
H donors	3		(1) ACD
Koc	1	pH 1	(1) ACD
Koc	1	pH 4	(1) ACD
Koc	1	pH 7	(1) ACD
Koc	1	pH 8	(1) ACD
Koc	1	pH 10	(1) ACD
logD	-3.31	pH 1	(1) ACD
logD	-2.81	pH 4	(1) ACD
logD	-2.81	pH 7	(1) ACD
logD	-2.84	pH 8	(1) ACD
logD	-3.66	pH 10	(1) ACD
logP	-0.311±0.646		(1) ACD
Molar Solubility	Very Soluble	pH 1	(1) ACD
Molar Solubility	Very Soluble	pH 4	(1) ACD
Molar Solubility	Very Soluble	pH 7	(1) ACD
Molar Solubility	Very Soluble	pH 8	(1) ACD
Molar Solubility	Very Soluble	pH 10	(1) ACD
Molecular Weight	178.57		(1) ACD
pKa	2.02±0.20	Most Acidic	(1) ACD

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pKa	9.14±0.20	Most Basic	(1) ACD
Vapor Pressure	1.45E-5 Torr	Temp: 25 °C	(1) ACD

Property	**Experimental Value**	**Condition**	**Note**
Melting Point	180-182 °C (decomp)	Solv: methanol (67-56-1)	(2) IC
Optical Rotatory Power	+139 °	Conc: 0.14 g/100mL Solv: water (7732-18-5) Temp: 20 °C	(2) IC

Notes:
(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)
(2) Mzengeza, Shadreck; Journal of Organic Chemistry 1988, V53(17), P4074-81

-- Resources --

References: ~295

STN Files: CAPLUS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CASREACT, CHEMCATS, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PROMT, RTECS, SYNTHLINE, TOXCENTER, USAN, USPATFULL

(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

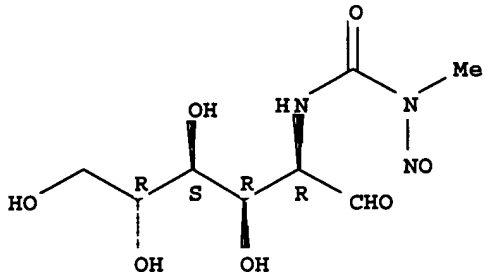
Database: REGISTRY

APPENDIX B

Compound: **Streptozotocin**

Registry Number: 18883-66-4

Absolute stereochemistry.



Formula: C8 H15 N3 O7

CA Index Name: D-Glucose, 2-deoxy-2-[[(methylnitrosoamino)carbonyl]amino]- (9CI)

Other Names: Glucopyranose, 2-deoxy-2-(3-methyl-3-nitrosoureido)-, D- (8CI); NSC 37917; NSC 85998; STRZ; STZ; Streptozocin; Streptozoticin; Streptozotocin; U 9889; Zanosar

-- Properties --

Property	Calculated Value	Condition	Note
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	1	pH 7	(1) ACD
Bioconc. Factor	1	pH 8	(1) ACD
Bioconc. Factor	1	pH 10	(1) ACD
H acceptors	10		(1) ACD
H donors	5		(1) ACD
Koc	3.43	pH 1	(1) ACD
Koc	3.44	pH 4	(1) ACD
Koc	3.42	pH 7	(1) ACD
Koc	3.29	pH 8	(1) ACD
Koc	1	pH 10	(1) ACD
logD	-1.55	pH 1	(1) ACD
logD	-1.55	pH 4	(1) ACD
logD	-1.55	pH 7	(1) ACD
logD	-1.56	pH 8	(1) ACD
logD	-2.27	pH 10	(1) ACD
logP	-1.546±0.766		(1) ACD
Molar Solubility	Soluble	pH 1	(1) ACD
Molar Solubility	Soluble	pH 4	(1) ACD
Molar Solubility	Soluble	pH 7	(1) ACD
Molar Solubility	Very Soluble	pH 8	(1) ACD
Molar Solubility	Very Soluble	pH 10	(1) ACD
Molecular Weight	265.22		(1) ACD
pKa	9.36±0.46	Most Acidic	(1) ACD

Notes:

APPENDIX B

(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)

-- Resources --

References: ~1885

STN Files: CAPLUS, ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HSDB, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PROMT, RTECS, TOXCENTER, USAN, USPAT2, USPATFULL, VETU

(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

Deleted Registry Number(s): 11006-80-7, 37793-00-3, 132769-73-4

Database: REGISTRY

TRA 1977514v1